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**Exercise prevents depression, but not anxiety. Results of
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Exercise prevents depression, but not anxiety. Results of the HUNT cohort study

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Abstract

Objectives

To address three questions; (a) does exercise provide protection against new onset depression and anxiety, (b) if so, what intensity and amount of exercise is required to gain protection and (c) what mechanisms underlie any association?

Method

A 'healthy' cohort of 33 908 adults, selected on the basis of having no symptoms of common mental disorder or limiting physical health conditions, were prospectively followed for 11 years. Validated measures of exercise, depression, anxiety and a range of potential confounding and mediating factors were collected.

Results

Undertaking regular leisure time exercise was associated with a reduced incidence of future depression, but not anxiety. The majority of this protective effect occurred at low levels of exercise and was observed regardless of intensity. After adjustment for confounders, the population attributable fraction suggests that, assuming the relationship is causal, 12% of future cases of depression could have been prevented if all participants had engaged in at least one hour of physical activity each week. The social and physical health benefits of exercise explained a small proportion of the protective effect. Previously proposed biological mechanisms, such as alterations in parasympathetic vagal tone, did not appear to have a role in explaining the protection against depression.

Conclusions

Regular leisure time exercise of any intensity provides protection against future depression, but not anxiety. Relatively modest changes in population levels of exercise may have important public mental health benefits and prevent a substantial number of new cases of depression.

Key words

Depression, anxiety, mental disorders, exercise, prevention, physical activity, public health

Introduction

The rising costs associated with depression and anxiety constitute a major public health problem across the developed and developing world (1). While the need to address the growing burden of these common mental disorders is not in doubt, there has been little consensus on how this should be executed. Although effective treatments are available, cost-effectiveness models suggest that even in the unlikely event of optimal treatment being delivered to all cases, only 35 to 50% of the overall burden of depression and anxiety would be alleviated (2). As a result, a number of agencies have begun to consider strategies aimed at primary prevention of both depression and anxiety.

Rose argued that the most appropriate method for preventing common, multifactorial diseases was to shift the entire population distribution of known risk factors (3). Such strategies are well established for the prevention of other conditions, such as cardiovascular disease. However, most of the known risk factors for depression and anxiety, such as familial risk, socioeconomic position and life events, are difficult or impossible to modify (4).

There is, however, some emerging evidence that lifestyle factors, such as physical inactivity, may be potential targets for strategies aimed at preventing depression and anxiety (5, 6). A variety of health surveys have demonstrated a cross sectional association between exercise and lower rates of both depression and anxiety (7, 8). However, the possibility of reverse causation (low mood or anxiety leading to reduced levels of exercise) has limited the interpretation of such studies. To date, the results of prospective studies have been more mixed. Some studies have found

no prospective association between levels of exercise and depression and anxiety (9-11), while others have suggested that any beneficial effects of exercise may be limited to certain subgroups or age groups, or only associated with intensive exercise (12-14). The evidence base has been further confused by many, but not all, of the published reports conflating depression and anxiety disorders despite each having unique risk factors and distinct biological processes (15). The evidence base for exercise as a treatment for current depression is more established, with numerous reviews concluding that exercise is moderately effective for reducing the symptoms of depression (16, 17). Recent analyses of the data used in these reviews have added further evidence for the anti-depressant effect of exercise with findings that both publication bias and enhanced control group responses may have led to an underestimate of the true effect size of exercise as an intervention in depression (18, 19). However, systematic reviews of the evidence for exercise in preventing new onset depression and/or anxiety have needed to be more tempered in their conclusions, particularly regarding the relative importance of the intensity and amount of exercise required to convey any protective effect (20).

A number of theories have been proposed as to how exercise may prevent mental illness, however, to date none of these have been formally evaluated in prospective epidemiological studies (5). Exercise is associated with a number of biological changes that could have an impact on mental health. One purported biological mechanism is alteration in the activity of the autonomic nervous system (ANS) (21, 22). Regular exercise increases parasympathetic vagal tone, leading to physiological changes such as resting bradycardia (23). Alterations in ANS activity have been observed in those suffering from depression and vagal nerve stimulation has been used to treat depression (21). Other explanations for any association

between exercise and depression and anxiety focus on the physical health, self-esteem or social benefits of exercise.

Addressing the uncertainty surrounding the relationship between exercise and depression and anxiety is important. While many agencies are keen to promote the potential mental health benefits of exercise, at present the literature is unable to provide the most basic information needed for effective, targeted, evidence-based public health campaigns concerning depression and anxiety. The aim of this study was to utilise a large ($n=33\,908$) prospective cohort to address three questions; (a) does exercise provide protection against new onset depression and anxiety, (b) if so, what intensity and total amount of exercise is required to gain protection and (c) what causal mechanisms underlie any association between exercise and later depression and anxiety?

Methods

Study design

The Health Study of Nord-Trøndelag County (HUNT study) represents one of the largest and most comprehensive population-based health surveys ever undertaken. The Nord-Trøndelag County of Norway covers a mainly rural area with a total population of 127 000 at the time of study commencement. In phase 1 (HUNT 1) of the study, conducted between January 1984 and February 1986, all inhabitants of the county aged 20 years or more ($N = 85\,100$) were invited to complete questionnaires on their lifestyle and medical history and attend a physical examination. A total of 74,599 individuals participated (87.7%). All participants were

then followed up 9 to 13 years later (between August 1995 and June 1997) in phase 2 of the study (HUNT 2). Detailed information on the HUNT cohort study has been published elsewhere (24, 25). The STROBE Checklist (online Supplemental File SA1) was followed throughout the study.

Selection of a 'healthy' sample

In order to be more confident regarding the direction of any associations found, data from HUNT 1 were used to select a 'healthy' cohort, without any evidence of current physical illness or depressive or anxiety disorders at baseline.

Symptoms of depression and anxiety at baseline

The presence of depression and anxiety at baseline (HUNT 1) was detected in two ways. Firstly, all participants completed 12-item anxiety and depression symptom index (ADI-12). This measure, designed to capture a range of symptoms suggestive of depression and anxiety, has been validated and shown to have a good test-retest correlation (26, 27). 60,980 respondents (81.7%) returned an adequately completed ADI-12. Previously, a cut-off at the 80th percentile of the total ADI-12 score has been used to define caseness (28). In order to be more conservative in creating a 'healthy' cohort only those falling below the 70th centile on total ADI-12 score were selected (n=42 686). Secondly, participants were also asked if they suffered from any impairments due to psychological complaints. An additional 726 individuals who indicated baseline psychological impairment were excluded.

Assessment of physical health at baseline

Physical ill-health may prevent individuals participating in exercise and is an independent predictor of common mental disorders (29). Participants were asked if they suffered any impairment to motor abilities or impairment due to physical illness, or suffered from, or have ever been diagnosed with diabetes, angina, myocardial infarction, stroke or cerebral haemorrhage. Consequently a further 8 444 participants were excluded, yielding a final 'healthy' cohort of 33 908 individuals.

Measurement of exercise at baseline

At the time of their baseline assessment (HUNT 1), all participants were asked how often they engaged in exercise (such as walking or swimming). They were provided with five options; never, less than once a week, once a week, two to three times a week and nearly every day. Participants were asked, on average, how long they exercised for on each occasion. By combining the answers for both of these questions, it was possible to produce an estimate of the total number of minutes per week each individual spent exercising. Participants were also asked about the intensity of their exercise, with three possible options; exercise without becoming breathless or sweating, exercise which results in breathlessness and sweating or practically exhausting themselves. The last two options were combined into one category.

The reliability and validity of these questions and a composite total time spent engaging in exercise per week has been demonstrated against three more objective measures of physical activity; VO₂ Max (maximal oxygen uptake), measures of body

position and motion over seven days using an ActiReg recording instrument and the International Physical Activity Questionnaire (IPAQ) (30).

Assessment of depression and anxiety in HUNT 2

At follow up (HUNT 2), all participants were asked to complete the Hospital Anxiety and Depression Scale (HADS) (31). The HADS is a self-report questionnaire comprising 14 four-point Likert-scaled items covering anxiety (HADS-A) and depression (HADS-D) symptoms over the last two weeks. A cut-off score of 8 in each subscale (HADS-A and HADS-D) has been found to be optimal for case finding, with sensitivity and specificity estimates of around 0.80 (32).

Potential confounding and mediating variables

In order to facilitate the differentiating of confounders and mediators, a conceptual hierarchical framework (see Figure 1) was constructed *a priori* to outline how various factors may relate to both exercise and depression and anxiety.

FIGURE 1. Theoretical Hierarchical Model Demonstrating How Potential Confounding and Mediating Factors May Interact With Both Levels of Exercise and Common Mental Disorders, specifically depression and anxiety.

Demographic and socio-economic factors

Information on participants' age, gender and marital status was obtained from the Norwegian National Population Registry. Participants were asked to record their

highest completed education level. Occupational social class was calculated according to the International Erikson-Goldthorpe-Portocareros classification (33).

Substance use

Participants were asked the total number of cigarettes consumed per day and how frequently they drank alcohol, with five options ranging from total abstainer to 10 or more times in the last week.

Body mass index

A specially trained nurse took measurements allowing the Body Mass Index (BMI) of each participant to be calculated.

New onset physical illness

The same somatic conditions and limitations that were used at baseline as exclusion measures were also assessed at follow up, allowing the identification of any new onset illnesses or impairments through the course of the study.

Autonomic nervous system (ANS) activity

Lowered resting pulse is a biological adaptation to regular exercise (34), due to increased parasympathetic vagal tone (23). At the HUNT 1 physical examination each participant's resting pulse was measured after at least four minutes of rest in the sitting position by palpation over the radial artery for 15 seconds.

Perceived social support

Each participant's perceived social support (both instrumental and emotional) was assessed via a single question; "If you fell ill and had to stay in bed for a significant period, how likely do you think it is that you would get the necessary help and support from family, friends or neighbours?" Five options were provided; very likely, quite likely, doubtful, unlikely, not likely at all.

Statistical analysis

All analyses were conducted using STATA statistical software, version 10.1 for Microsoft Windows (35). A multiple imputation model was constructed to replace missing values using the imputations by chained approach (ICE) method. Thirty imputed data sets were created. All variables used in the analyses were included in the imputation model. Sensitivity analyses utilising complete case analysis were undertaken to ensure results were not significantly altered by the multiple imputation process.

The associations between level of physical activity and both depression and anxiety were assessed using univariate and then multivariate logistic regression. The total amount of exercise undertaken each week was divided into six categories ranging from none up to more than four hours. The relative confounding effect of each of the variables outlined above was examined in turn, before a final multivariate model containing all potential cofounders was constructed. Interactions by gender, age subgroup and exercise intensity were tested for using post-estimation Wald tests. The correlation between levels of exercise at baseline and follow up was examined using Spearman's rank-order correlation tests. In addition to reporting odds ratios,

the relative importance of exercise in predicting future depression and anxiety was examined using population attributable fractions (PAFs).

Finally, the importance of three potential mediating factors were considered: new onset physical illness, ANS activity (resting pulse) and the level of perceived social support. Although a 'healthy' cohort was selected for this study, the possibility of reverse causation remained, with sub-threshold symptoms of depression and anxiety leading to reduced levels of exercise. Therefore, a fourth potential pathway, reverse causation, was also considered. The associations between each of the four potential mediating factors and both exercise levels and depression and anxiety were examined using linear regression, before the impact of adding each potential mediating factor to a final model was assessed.

Ethics

Both the HUNT 1 and the HUNT 2 study were approved by the National Data Inspectorate and the Board of Research Ethics in Health Region IV of Norway.

Results

Description of the sample

The characteristics of the 'healthy' cohort of 33 908 individuals are described in Table 1. Of these, 22 564 (66.5%) were successfully followed up at HUNT 2. Females ($p<0.001$) and younger participants ($p<0.0001$) were more likely to be followed up. The frequency of exercise undertaken at baseline did not predict loss to follow up once the impact of gender and age was considered ($p=0.19$). Of the 22 564 individuals followed up, 1 578 (7.0%) developed case-level symptoms of depression and 1 972 (8.7%) developed case-level symptoms of anxiety. All participants gave their informed consent to participate in this study.

Exercise at baseline and new onset depression and anxiety

There was a negative relationship between the total amount of exercise undertaken at baseline and risk of future depression ($p=0.001$). In contrast, the prevalence of case-level anxiety was similar regardless of the levels of baseline exercise ($p=0.21$). Table 2 displays logistic regression models of the associations between the total amount of exercise at baseline and later depression and anxiety. After adjustment for a range of confounders, those who reported undertaking no exercise at baseline had a 44% (95% confidence interval 17 to 78%) increased odds of developing case-level depression compared to those who were exercising one to two hours a week. The models presented in Table 2 confirm the lack of any association between baseline exercise levels and later case-level anxiety ($p=0.27$).

There was no evidence of interaction by gender ($p>0.2$ for all) or when stratified by age group (greater than or less than 50 years; $p=0.96$) in the association between total amount of exercise at baseline and later case-level depression or anxiety. A similar significant association was seen between baseline levels of exercise and later depression in those aged less than 50 years ($p=0.04$) and those aged 50 years and over ($p=0.03$). As expected, there was a significant correlation between the amount of exercise undertaken at baseline and follow up ($p<0.001$).

Dose-response relationship

Figure 2 provides visual representations of the dose-response relationship between total exercise at baseline and the odds of later case-level depression. Most of the protective effect of exercise is realized with relatively low levels of exercise, with no indication of any additional benefit beyond one hour of exercise each week. Maximum likelihood ratio tests suggest that an exponential decay model (with decreasing benefit as the total time of exercise increases) was a better fit for the data than a linear model (test for difference between models, $p=0.004$). The combined PAF for less than one hour per week was 11.9%. There was no evidence of an interaction by intensity of exercise ($p=0.96$).

FIGURE 2. Adjusted Odds Ratios^a (with 95% confidence intervals) for Case-level Depression at Follow Up According to the Overall Amount of Exercise Reported at Baseline.

^a All odds ratios are adjusted for age, gender, marriage status, education, social class, number of cigarettes, alcohol use and body mass index.

Possible mediating pathways

In line with *a priori* predictions, those who engaged in less exercise at baseline tended to have higher resting pulse, lower levels of perceived social support, more sub-threshold symptoms of depression and anxiety and were more likely to develop new onset physical illnesses over the course of the study ($p < 0.001$). Table 3 demonstrates that three of the four potential mediating pathways considered accounted for some of the observed association; reverse causation, lower levels of perceived social support and new onset physical illness. However, each of these modelled pathways explained only a very small proportion of the observed effect, with the majority of the protective effect of exercise remaining unaccounted for by measured factors.

Discussion

Using a large population cohort study we have observed that relatively small amounts of exercise can provide significant protection against future depression, but not anxiety. This protective effect is seen equally across all groups, regardless of the intensity of exercise that is undertaken or the gender or age of participants. Assuming there is no residual confounding in our final model and the observed relationship is causal, our results suggest that if all participants had exercised for at least one hour each week, 12% of the cases of depression at follow up could have been prevented.

The key strengths of this study are its large sample size, prospective data collection, use of validated measures of physical activity and mental disorder and the detailed

information available on a wide range of potential confounding and mediating factors. Despite these strengths, the analyses presented have some important limitations. Regarding study design, whilst individuals reporting current symptoms and/or impairment of depression or anxiety at baseline were excluded using a two-step process, we were not able to exclude individuals with a history of prior episodes of depression and anxiety. Thus, it is possible that some individuals with a lifetime history of depression or anxiety may have been included in the “healthy” cohort, so that a proportion of the future cases may be recurrent episodes of depression or anxiety. While the long follow up time is a strength, the use of a single measure of relapsing and remitting conditions such as depression means that some misclassification will have occurred. Such misclassification is likely to be random and therefore result in regression dilution bias and an attenuation of effect sizes. This has important consequences for the interpretation of results and suggests that the real protective effect of exercise may be even greater than that reported in this paper. The measurement of exercise at a single time point will also have created some misclassification, although there was a significant correlation between levels of exercise at baseline and follow up. The majority of other limitations relate to the measures used. While the HADS is one of the most widely used and validated measures of depression and anxiety, the operationalization of any mental disorder via a self-report screening tool cannot be considered equivalent to a clinical diagnosis and a risk of misclassification remains. Similarly, while the measures of exercise used have been extensively validated (30), they remain reliant on self-report and each factor considered in the analysis of mediation was measured with a single item that may not have fully captured the constructs being considered. In addition to standard regression, population attributable fractions (PAF) were used to describe the relative importance of exercise as a possible preventative strategy.

PAFs can be a useful way to help guide public health interventions, but any estimates of PAF assume a causal relationship with no residual confounding. While attempts were made to account for many confounders, a number of important potential confounding variables, such as personality, attitude to health, diet, seasonal weather variations and the degree to which each participant's local environment is conducive to regular exercise remained unmeasured. The Nord-Trøndelag County is situated between Northern Latitudes 63° and 65°. As a result, there is considerable seasonal variation in the number of daylight hours. Previous studies have shown an associated seasonal variation in depression prevalence within Nord-Trøndelag County, with higher rates of depression between December and April (36). If rates of physical activity were also lower in the winter months, then the confounding effect of the season at the time of assessment could impact on any observed cross sectional association between exercise and depression. However, this longitudinal study mitigates against this by the fact that there was no link between the seasonal timing of the assessments in HUNT 1 (when exercise levels were measured) and HUNT 2 (when levels of depression were assessed). The invitation for participation in HUNT 2 was sent to all residents of the County at a time that was unrelated to when each individual had been assessed during HUNT 1. The equal popularity of both winter and summer sports in Norway will also have reduced the possibility of seasonal confounding.

This study represents the largest and most detailed modelling of the prospective dose-response relationship between exercise and depression and the first published epidemiological exploration of the causal pathways involved. In addition to confirming that more active individuals are less likely to develop depression, we were able to demonstrate that this was most accurately modeled as an exponential

decay model, with decreasing benefit as the total time spent exercising increases. This supports and expands on the tentative conclusions from a recently published review, which highlighted that substantial mental health benefits may be gained from relatively moderate levels of exercise (37). Importantly, the majority of the protective effects of exercise against depression are realized within the first hour of exercise undertaken each week, which provides some clues regarding causation and has major implications for possible future public mental health campaigns. The majority of studies examining the role of physical activity in preventing cardiovascular disease have found that the beneficial cardiovascular effects continue to increase up to around two to three hours of exercise per week (38, 39). Thus, while there are similarities in the overall shape of the dose-response relationship between exercise and depression and exercise and somatic illness, the level of activity needed to realize the bulk of the possible protective effects are very different. Our finding that more vigorous intensity exercise had no additional protective effects against future case-level depression is also in contrast to previous findings regarding protective factors against cardiovascular disease (39).

Taken together, these results suggest that processes such as alterations in ANS activity and modification of metabolic factors, which require more regular or strenuous exercise, may be less important when considering the protective effects of exercise against future depressive illness. In keeping with this hypothesis, our results suggest that the perceived social benefits of exercise may mediate some of the protective effects against depression. However, within our analysis the increased levels of perceived social support accounted for only a small proportion of the effect observed, meaning the bulk of the observed protective effect remains unexplained. An individual's perception of their social support may be subject to bias

relating to their current mental state. This type of reporting bias could lead to an over-estimate of the mediating effect of perceived social support, meaning an even greater proportion of the observed protective effect of exercise may be unexplained. We propose two possible explanations to account for the unexplained protective effect of exercise. Firstly, the remaining prospective associations may be due to confounding from factors not measured, such as shared genetic factors, personality or individual attitudes to health (40). Alternatively, there may be other causal factors not measured in this study, such as changes in self-esteem, serotonin release (41), increased expression of neuroprotective proteins such as brain-derived neurotrophic factor (BDNF), altered hippocampal neurogenesis or modifications to the activity levels of the hypothalamic-pituitary-adrenal (HPA) axis (42). The lack of any association between exercise and future anxiety disorders suggests that the link between exercise and depression is not merely related to a general increase in mental well-being and is unlikely to involve risk factors shared between depression and anxiety.

Despite the remaining uncertainty regarding causal pathways, the findings presented in this study have important public health implications. There is evidence that levels of exercise in the general population of developed countries has decreased considerably over the recent decades (43), with similar trends now also being observed in developing countries. The results of this study indicate that relatively modest increases in the overall amount of time spent exercising per week may be able to prevent a substantial number of new cases of depression. If causality is assumed and there are no other major cofounders, our results suggest that at least 12% of new cases of depression could be prevented if all adults participated in at least one hour of exercise each week. While education regarding the higher levels

of exercise required to achieve maximum cardiovascular and metabolic benefits remain important, informing individuals that significant mental health benefits may be achieved with small changes in their behaviour may be valuable in facilitating behavioural change. Given that the intensity of exercise does not appear to be important, it may be that the most effective public health measures are those that encourage and facilitate increased levels of everyday activities, such as walking or cycling. The results presented in this study provide a strong argument in favour of further exploration of exercise as a strategy for the prevention of depression.

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Authors' contribution

SBH conceptualised and planned this study together with AM, SO and MH. The analysis was carried out by SBH, with assistance from AM, SO and SLH. This paper was written by SBH, with SO, SLH, SW, AM and MH assisting with the interpretation of results and providing detailed comments on earlier drafts. SBH is guarantor.

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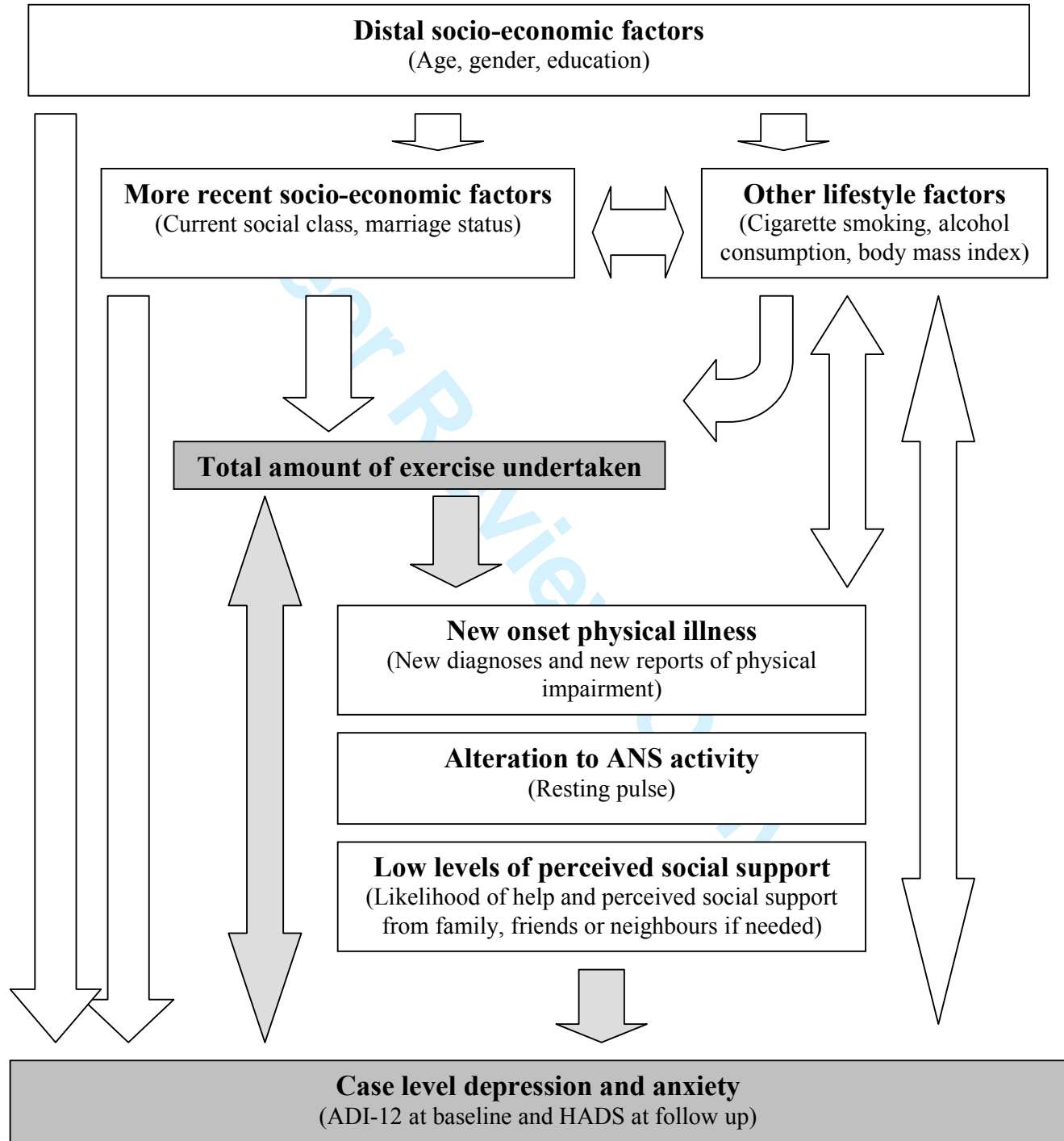
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FIGURE 1. Theoretical Hierarchical Model Demonstrating How Potential Confounding and Mediating Factors May Interact With Both Levels of Exercise and Common Mental Disorders.

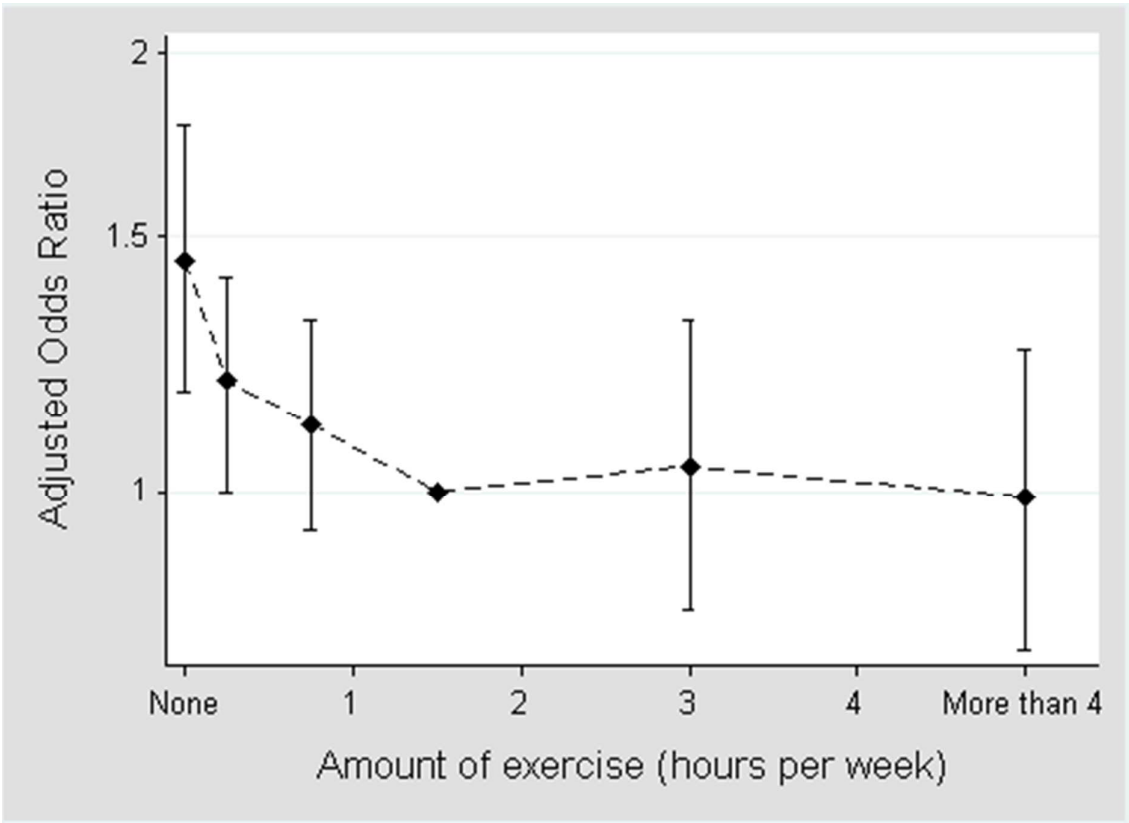


ANS = Autonomic Nervous System

ADI-12 = Anxiety and Depression Symptom Index

HADS = Hospital Anxiety and Depression Scale

FIGURE 2. Adjusted Odds Ratios^a (with 95% confidence intervals) for New Case-level Depression at Follow Up According to the Overall Amount of Exercise Reported at Baseline.



^a All odds ratios are adjusted for age, gender, marriage status, education, social class, number of cigarettes, alcohol use and body mass index.

TABLE 1: Description of the 'Healthy' Cohort of Individuals Followed Prospectively From HUNT 1 to HUNT 2.

Variable	N		Frequency	
			N ^a	Percentages ^b
Gender	33908	Male	17118	50.5
		Female	16790	49.5
Age	33908	Mean, SD (years)	45.2 (mean)	16.5 (SD)
Marital status	33690	Married/reg partnership	24004	71.3
		Unmarried	6931	20.6
		Divorced/separated	857	2.5
		Widowed	1898	5.6
Highest education	32978	Compulsory (Primary)	18064	54.8
		Secondary School	10900	33.1
		University	4014	12.2
Social class ^c	30406	Higher grade professionals	2425	8.0
		Lower grade professionals	3960	13.0
		Non-manual employees	6261	20.6
		Small proprietors/farmers	6973	22.9
		Lower grade technicians	3697	12.2
		Manual workers	4964	16.3
		Not in employment	2126	7.0
Cigarette use	32579	Mean, SD	3.6 (mean)	6.1 (SD)
Alcohol consumption ^d	33270	Total abstainer	2991	9.0
		None (but not total abstainer)	14348	43.1
		1 – 4 times	14052	42.2
		5 – 10 times	952	2.9
		More than 10 times	927	2.8
Body Mass Index	33850	Mean, SD	24.9 (mean)	3.7 (SD)
Total amount of exercise per week	27136	None	3390	12.5
		Up to 30 minutes	6841	25.2
		31 to 59 minutes	6508	24.0
		One to two hours	5423	20.0
		Two to four hours	2579	9.5
		More than 4 hours	2395	8.8

^a All values indicate N (number of participants), unless otherwise indicated in parentheses.

^b All values provided are percentages, unless otherwise indicated in parentheses.

^c Based on current occupation.

^d Frequency in last 14 days.

TABLE 2: Prospective Associations Between Total Amount of Exercise at Baseline and Later New Common Mental Disorder

Total amount of exercise per week	Depression ^{a,b}		Anxiety ^{a,b}	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Model 1 (Adjusted for age and gender) ^c				
None	1.69	(1.39 – 2.06)	1.16	(0.96 – 1.41)
Up to 30 minutes	1.29	(1.10 – 1.52)	1.16	(0.99 – 1.35)
31 to 59 minutes	1.14	(0.96 – 1.35)	1.15	(0.99 – 1.34)
1 to 2 hours	1.00		1.00	
2 to 4 hours	1.08	(0.86 – 1.35)	1.20	(0.98 – 1.45)
More than 4 hours	1.03	(0.81 – 1.29)	1.21	(0.99 – 1.48)
Model 2 (+ sociodemographics) ^d				
None	1.53	(1.25 – 1.88)	1.09	(0.90 – 1.33)
Up to 30 minutes	1.23	(1.04 – 1.45)	1.11	(0.95 – 1.29)
31 to 59 minutes	1.12	(0.95 – 1.33)	1.13	(0.97 – 1.32)
1 to 2 hours	1.00		1.00	
2 to 4 hours	1.04	(0.83 – 1.31)	1.18	(0.97 – 1.44)
More than 4 hours	0.98	(0.78 – 1.24)	1.20	(0.98 – 1.47)
Model 3 (+ cigarette and alcohol use) ^e				
None	1.47	(1.19 – 1.80)	1.03	(0.85 – 1.26)
Up to 30 minutes	1.20	(1.02 – 1.42)	1.07	(0.92 – 1.25)
31 to 59 minutes	1.11	(0.94 – 1.32)	1.12	(0.96 – 1.30)
1 to 2 hours	1.00		1.00	
2 to 4 hours	1.04	(0.83 – 1.31)	1.18	(0.97 – 1.44)
More than 4 hours	0.97	(0.77 – 1.23)	1.20	(0.98 – 1.47)
Model 4 (+ body mass index) ^e				
None	1.52	(1.24 – 1.86)	1.09	(0.90 – 1.33)
Up to 30 minutes	1.22	(1.03 – 1.44)	1.11	(0.95 – 1.29)
31 to 59 minutes	1.12	(0.95 – 1.33)	1.13	(0.97 – 1.31)
1 to 2 hours	1.00		1.00	
2 to 4 hours	1.05	(0.83 – 1.32)	1.18	(0.97 – 1.44)
More than 4 hours	0.99	(0.79 – 1.25)	1.20	(0.98 – 1.47)
Model 5 (Adjusted for all of above) ^f				
None	1.44	(1.17 – 1.78)	1.03	(0.84 – 1.26)
Up to 30 minutes	1.19	(1.00 – 1.40)	1.07	(0.92 – 1.25)
31 to 59 minutes	1.11	(0.94 – 1.31)	1.12	(0.96 – 1.30)
1 to 2 hours	1.00		1.00	
2 to 4 hours	1.04	(0.83 – 1.31)	1.18	(0.97 – 1.44)
More than 4 hours	0.99	(0.78 – 1.25)	1.21	(0.99 – 1.48)
p value for trend in final model	0.003		0.27	

^a Figures are adjusted odds ratios (to 2 d.p.) (95% confidence interval) compared to those exercising one to two hours a week.

^b 95% confidence intervals are provided in the right-hand column in parentheses.

^c Model 1 adjusts for age and gender.

^d Model 2 adjusts for age, gender, marriage status, education and social class.

^e Models 3 and 4 adjust for sociodemographics (model 2) plus the stated covariates.

^f Model 5 adjusts for age, gender, marriage status, education, social class, number of cigarettes, alcohol use and body mass index.

TABLE 3: Additional Multivariable Models to Investigate Possible Mediating Pathways Between Total Amount of Exercise at Baseline and Later New Case-level Depression

Total amount of exercise per week	Depression ^f		p value ^e
	Odds Ratio	95% CI	
Model 1 (Adjusted for measured confounders) ^a			
None	1.44	(1.17 – 1.78)	0.004
Up to 30 minutes	1.19	(1.00 – 1.40)	
31 to 59 minutes	1.11	(0.94 – 1.31)	
1 to 2 hours	1.00		
2 to 4 hours	1.04	(0.83 – 1.31)	
More than 4 hours	0.99	(0.78 – 1.25)	
Model 2 (+ baseline symptoms (ADI-12 ^b)) ^c			
None	1.40	(1.13 – 1.73)	0.04
Up to 30 minutes	1.13	(0.96 – 1.34)	
31 to 59 minutes	1.07	(0.90 – 1.26)	
1 to 2 hours	1.00		
2 to 4 hours	1.09	(0.86 – 1.37)	
More than 4 hours	1.07	(0.85 – 1.36)	
Model 3 (+ resting pulse) ^c			
None	1.48	(1.20 – 1.82)	0.002
Up to 30 minutes	1.21	(1.02 – 1.43)	
31 to 59 minutes	1.12	(0.95 – 1.33)	
1 to 2 hours	1.00		
2 to 4 hours	1.04	(0.83 – 1.31)	
More than 4 hours	0.98	(0.78 – 1.24)	
Model 4 (+ likelihood of help and perceived social support from family, friends or neighbours) ^c			
None	1.42	(1.15 – 1.76)	0.007
Up to 30 minutes	1.18	(1.00 – 1.40)	
31 to 59 minutes	1.11	(0.94 – 1.31)	
1 to 2 hours	1.00		
2 to 4 hours	1.04	(0.83 – 1.31)	
More than 4 hours	0.98	(0.78 – 1.24)	
Model 5 (+ new onset physical illness) ^d			
None	1.38	(1.11 – 1.71)	0.02
Up to 30 minutes	1.16	(0.98 – 1.37)	
31 to 59 minutes	1.09	(0.92 – 1.30)	
1 to 2 hours	1.00		
2 to 4 hours	1.02	(0.81 – 1.29)	
More than 4 hours	0.97	(0.76 – 1.22)	

^a Model 1 adjusts for age, gender, marriage status, education, social class, number of cigarettes, alcohol consumption and body mass index.

^b ADI-12: Anxiety and Depression Symptom Index.

^c Models 2, 3, 4 and 5 adjust for sociodemographics (model 1) plus stated covariate.

^d In Model 5 the sum of new diagnoses and the level of new impairment are added as separate variables.

^e Post-estimation Wald test.

^f Figures are adjusted odds ratios (to 2 d.p) (95% confidence interval) compared to those exercising one to two hours a week. 95% confidence intervals are provided in the right-hand column in parentheses.